REMARKS

Applicants have changed the legal representation of this application under the terms of an exclusive license recently executed by assignee Cedars Sinai Medical Center to BBB Biotechnologies, Inc. ("BBB"). As a result of the change of representation and the execution of the exclusive license to BBB, Applicants desire to amend the allowed claims by (i) dividing the allowed subject matter into two separate applications, wherein the claims of this application are now limited to use of an ATP-sensitive potassium channel agonist to selectively increase the permeability of the cells of an abnormal brain region to a medicant compared to normal brain regions, and wherein the use of a calcium-activated potassium channel agonist to accomplish the same goal is submitted in a separate continuation application; and (ii) dividing the previously allowed dependent claims covering a number of medicants, disease states, and other subject matter into separate claims.

Claims specifically directed to the use of minoxidil sulfate have been added, including claims 110, 153, 154, 168 and 195. Support for these claims is found in the specification, for example, at page 10. Claims specifically directed to the use of diazoxide have also been added, including claims 111, 171 and 199. Support for these claims is found in the specification, for example, at page 10. Claims 121, specifying particular types of abnormal brain regions including glioma, glioblastoma, oligodendroglioma, astrocytoma, ependymoma, primitive neuroectodermal tumor, atypical meningioma, malignant melanoma, neuroblastoma, sarcoma, melanoma, lymphoma and carcinoma, has been added. Support for this claim can be found in the specification, for example, on page 10. Claims have also been added that are specifically directed to antigen-antibody fragments as a medicant, including claims 125, 178 and 186. Support for these claims can be found in the specification, for example, at page 13. Claim 185, specifically directed to tumor necrosis factor-α, has been added. Support for this claim can be found in the specification, for example, on page 13.

After entry of the amendment, claims 1-6, 11-18, 97-100, 106-109 and 110-199 remain pending. Claims 7-10, 19-96 and 101-105 have been canceled. Claims 1-6, 11-18 and 110-152 are directed to a method of delivering a medicant to an abnormal brain region comprising administering an ATP-sensitive potassium channel agonist and a medicant. Claims 153 -166 are directed to a method of delivering a medicant to an abnormal brain region comprising administering minoxidil or minoxidil sulfate and a medicant.

Claim 97 as allowed was directed generally to a pharmaceutical composition that included a combination of a calcium-activated or ATP-sensitive potassium channel agonist (other than bradykinin or a bradykinin analog) formulated in a pharmaceutical solution together with a medicant for delivery by infusion or injection into a mammal. Several references disclosed in the IDS filed on April 21, 2000 and the Supplemental IDS filed on May 23, 2002 taught the combination of a potassium channel agonist and a drug for parenteral delivery, understood in the art to include intravascular infusion or injection. U.S. Patent No. 5,679,706 is directed to a composition comprising a potassium channel opener in combination with a class II anti-arrhythmia compound. U.S. Patent No. 5,578,599 is directed to a composition comprising minoxidil in combination with a 5-alpha reductase inhibitor. U.S. Patent No. 5,262,419 discloses a potassium channel agonist in combination with an anti-inflammatory drug. Pending claims 97-100 and 167-177 are directed to a pharmaceutical composition including a combination of an ATP-sensitive potassium channel agonist and a therapeutic cytotoxic agent. Claims 177-194 are directed to a pharmaceutical composition comprising an ATP-sensitive potassium channel agonist and a drug. Applicants believe that the claims as now presented overcome this art.

The Examiner originally rejected and then allowed the previously presented claims over the combination of Black et al. (U.S. Patent No. 5,434,137) in view of Sobey et al. (Sobey, G.C. et al., Stroke 28 (11):2290-4 (1997) and Cherskey (U.S. 5,234,947). Applicants' new counsel agree that the previously presented claims are patentable over this combination of references. Applicants further point out that neither Black '137 nor Sobey address the use of an ATP-sensitive potassium channel agonist, and thus neither is directly relevant to the claims as now limited.

Further, new counsel takes the opportunity to note that Sobey merely concluded that reactive oxygen species activate calcium-activated potassium channels. In particular, Sobey found that dilatation of normal brain microvasculature (i.e., cerebral arterioles) by hydrogen peroxide (provided to rat arterioles exogenously or produced endogenously) is mediated by the activation of calcium-dependent potassium channels. Sobey did not address (i) any means to accomplish any selective increase in permeability of abnormal brain microvasculature over normal vasculature; or (ii) whether calcium-activated potassium channels can be activated to consistently mediate vasodilatation, much less selective brain vasculature permeability, in the absence of a source of hydrogen peroxide or other reactive oxygen species. The observation by Sobey that bradykinin produces endogenous hydrogen peroxide which activates calcium-

dependent potassium channels which then causes vasodilatation simply cannot be extrapolated to a conclusion that another calcium-dependent potassium channel activator that does not act by producing hydrogen peroxide endogenously would have the same effect on the channel.

Cloughesy et al. (copy provided and cited in the Supplemental Information Disclosure Statement submitted herewith), co-authored by one of the Applicants (Keith Black), stated in 1995 that "[v]asoactive agents, including leukotrienes, bradykinin, and histamine, appear to selectively increase permeability." Vasoactive agents are known to include both vasodilators and vasoconstrictors. Cloughesy et al. did not mention or address the use of any ATP-sensitive potassium channel agonists, as presently claimed, nor did the reference teach or suggest their use to selectively increase permeability of abnormal brain tissue.

Finally, Applicants submit a Supplemental Information Disclosure Statement to cite additional references known to new counsel and/or Applicants.

CONCLUSION

In light of the amendments and comments presented herein, Applicants request that the Examiner allow all pending claims.

Respectfully submitted,

Sherry M. Knowles, Esq.
Reg. No. 33,052

King & Spalding
191 Peachtree St.
Atlanta, Georgia 30303
404-572-3541
404-572-5145 (fax)